

# Improved glycemic control and reduced bodyweight with exenatide: A double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks

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## ABSTRACT

**Aims/Introduction:** To evaluate the efficacy and safety of the glucagon-like peptide-1 receptor agonist, exenatide, in Japanese patients with type 2 diabetes mellitus suboptimally controlled despite therapeutic doses of a sulfonylurea alone or combined with a biguanide or thiazolidinedione.

**Materials and Methods:** Patients were randomized to a placebo or exenatide, either 5 or 10 µg, given subcutaneously b.i.d. in addition to oral therapy. Patients randomized to 10 µg exenatide received 5 µg b.i.d. for the first 4 weeks, followed by 10 µg b.i.d. for the last 20 weeks.

**Results:** A total of 179 patients received the study drug and composed the full analysis set ( $n = 35$ , placebo;  $n = 72$ , exenatide 5 µg;  $n = 72$ , exenatide 10 µg; 68% male;  $58 \pm 10$  years; body mass index  $25.5 \pm 4.1$  kg/m<sup>2</sup>; HbA<sub>1c</sub>  $8.2 \pm 0.9\%$ ; means  $\pm$  standard deviations). Baseline to end-point (least-squares means  $\pm$  standard errors) HbA<sub>1c</sub> changes (%) were  $-0.28 \pm 0.15$  (placebo),  $-1.34 \pm 0.11$  (exenatide 5 µg) and  $-1.62 \pm 0.11$  (exenatide 10 µg) (both  $P < 0.001$ , exenatide vs placebo). Baseline to end-point bodyweight changes (kg) were  $-0.47 \pm 0.39$  (placebo),  $-0.39 \pm 0.28$  (exenatide 5 µg) and  $-1.54 \pm 0.27$  (exenatide 10 µg;  $P = 0.026$ , exenatide 10 µg vs placebo). Nausea, generally mild to moderate, was reported in 8.6% (placebo), 25.0% (exenatide 5 µg) and 36.1% (exenatide 10 µg) of patients. Mild to moderate hypoglycemia was reported in 22.9% (placebo), 51.4% (exenatide 5 µg) and 58.3% (exenatide 10 µg) of patients.

**Conclusions:** Over 24 weeks, exenatide vs the placebo improved glycemic control, reduced bodyweight (10 µg) and was well tolerated in Japanese patients with type 2 diabetes mellitus suboptimally controlled, despite oral therapy including a sulfonylurea. This trial was registered with ClinicalTrials.gov (no. NCT00577824). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2010.00084.x, 2011)

**KEY WORDS:** Exenatide, Glycemic control, Japanese

## INTRODUCTION

The number of diabetes patients in Japan is growing. According to an 'Outline of the National Health and Nutrition Survey, Japan 2006', which was carried out by The Health Service Bureau, Ministry of Health, Labor and Welfare, approximately 8.2 million people are strongly suspected of having diabetes (HbA<sub>1c</sub>  $\geq 6.1\%$ ), the estimated population reaching approxi-

mately 18.7 million when those who cannot deny the possibility of having diabetes ( $6.0\% \geq \text{HbA}_{1c} \geq 5.6\%$ ) are included<sup>1</sup>. Japanese type 2 diabetes mellitus patients are less obese with the 'thrifty' genotype, which causes more insulin secretion deficiency and less insulin resistance than Westerners<sup>2</sup>.

Exenatide is the first in a class of anti-diabetic agents known as glucagon-like peptide-1 (GLP-1) receptor agonists. Exenatide, which is a 39-amino acid peptide, shares several metabolic effects with endogenous GLP-1, including glucose-dependent stimulation of insulin secretion<sup>3</sup>, suppression of glucagon secretion<sup>4</sup>, slowing of gastric emptying<sup>5</sup>, and increasing satiety resulting in reduction of food intake and improving  $\beta$ -cell function<sup>6,7</sup>. Because abnormal  $\beta$ -cell function has been recognized as a major factor for the development of type 2 diabetes mellitus in Japanese

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patients<sup>8</sup>, exenatide might be beneficial for those Japanese patients.

A randomized, double-blind, placebo-controlled, parallel phase 2 study has previously evaluated the dose-dependent effects on glycaemic control and safety of 2.5, 5 and 10 µg exenatide over a period of 12 weeks in 153 Japanese patients whose type 2 diabetes mellitus was suboptimally controlled despite therapeutic doses of sulfonylurea (SU), biguanide (BG) or thiazolidine derivative (TZD). That study showed that, at doses up to 10 µg b.i.d., exenatide reduced plasma glucose in a dose-dependent manner and was generally well tolerated<sup>9</sup>.

In the present study, we investigated safety and efficacy of exenatide in Japanese patients with suboptimally controlled type 2 diabetes mellitus over 24 weeks. This is the first phase 3 study of exenatide in Japanese patients with type 2 diabetes mellitus.

## SUBJECTS AND METHODS

### Subjects

Japanese patients were included if they were between 20 and 75 years-of-age and had been diagnosed with type 2 diabetes mellitus according to the classifications by the Japan Diabetes Society and World Health Organization, and with body-weight  $\geq 50$  kg. Patients were required to have been treated with SU monotherapy, combination therapy with SU and BG, or SU and TZD without any dose change for 90 days before screening. Patients on  $\alpha$ -glucosidase inhibitors ( $\alpha$ -GI) or short-acting insulin secretion inducers at the time of screening could be included in the present study, but had to be discontinued and washed-out for a period of 2–3 weeks.

Patients had inadequate glycaemic control, as shown by HbA<sub>1c</sub>  $\geq 7.0\%$  and  $\leq 10.0\%$  at screening. Exclusion criteria included treatment with any exogenous insulin or drug directly affecting gastrointestinal motility within 90 days before screening, a clinically significant gastrointestinal disorder or hepatic disorder, serum creatinine  $\geq 1.5$  mg/dL in men or  $\geq 1.4$  mg/dL in women, and fasting plasma glucose (FPG)  $\geq 250$  mg/dL or casual blood glucose  $\geq 350$  mg/dL or at least one episode of severe hypoglycemia. Female patients of childbearing age were excluded if they were pregnant at the time of enrolment, intended to become pregnant during the study, had not practiced a reliable method of birth control for 90 days before screening or did not agree to continue practicing a reliable method of birth control during the study.

This study was carried out in 23 centers in Japan. Patients, investigators and the sponsor were unblinded to the injection volume, but blinded to the identity of exenatide and the placebo. Of 211 screened patients, 181 fulfilled inclusion/exclusion criteria (one patient decided to withdraw and 29 patients didn't meet inclusion/exclusion criteria) and were randomly assigned (1:2:2) to subcutaneous injection of placebo, 5 µg exenatide or 10 µg exenatide b.i.d. using a dynamic allocation algorithm that involved stratification factors including HbA<sub>1c</sub> value and prior use of  $\alpha$ -GI. Patients randomized to exenatide 10 µg b.i.d. received 5 µg b.i.d. for the first 4 weeks, followed by 10 µg

twice daily for the last 20 weeks. Following randomization, all patients were instructed to self-administer the study drug into the abdomen within 60 min before their morning and evening meals.

Institutional review boards provided written approval of the study protocol and the informed consent document. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki and was consistent with good clinical practices and applicable laws and regulations. Investigators obtained written informed consent from patients before carrying out protocol procedures. The study also included an open-label extension period to 52 weeks, which will be reported separately.

### Study End-points

The primary end-point was a change in HbA<sub>1c</sub> from baseline to end-point (week 24 or last available observation on the treatment). All HbA<sub>1c</sub> values used in the present study were Japan Diabetes Society values. Secondary end-points included: the percentage of patients who achieved HbA<sub>1c</sub>  $< 7.0\%$  or  $< 6.5\%$  at end-point (only patients with a baseline HbA<sub>1c</sub>  $\geq 7\%$  or  $\geq 6.5\%$  were eligible for the analysis), changes from baseline to end-point of FPG, bodyweight, serum lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), 7-point self-monitored blood glucose (SMBG) levels (before breakfast, lunch and dinner, at 2 h after starting each meal and before bedtime), markers of insulin secretion, resistance and glycaemic control (homeostasis model assessment beta cell function [HOMA-B], homeostasis model assessment insulin resistance [HOMA-R], 1,5-anhydroglucitol), and safety. Safety measures included treatment-emergent adverse events (TEAE) including hypoglycemia and antibodies to exenatide. Hypoglycemia was defined as the presence of any signs or symptoms of hypoglycemia, regardless of blood glucose concentration. Hypoglycemia events that showed a blood glucose level of  $< 70$  mg/mL without signs and symptoms were collected with the designation of 'blood glucose decreased'. Hypoglycemia that required the assistance of another person was considered as severe hypoglycemia. If hypoglycemia symptoms occurred, the investigators instructed the subjects to measure blood glucose using the blood glucose meter for self-monitoring. In addition, patients were instructed to notify the principal investigator if any hypoglycemia symptoms occurred or if their blood glucose level was  $< 70$  mg/dL. If a dosage of SU reduction was deemed appropriate by the investigator, the dosage was reduced to 50% or less of the dose at the time of the reported events.

### Assays

Antibodies to exenatide were measured using a solid-phase enzyme-linked immunosorbent assay as previously described<sup>10</sup>.

### Statistical Analyses

Data are presented for the full analysis set (FAS), which includes all randomized patients who received at least one dose of study

drug and who had post-baseline data available. All tests of treatment effects were carried out at a two-sided significance level of 5%, unless otherwise stated. Unless otherwise stated, data are presented as mean  $\pm$  standard deviation (SD).

The primary end-point was change in HbA<sub>1c</sub> from baseline to end-point. Change in HbA<sub>1c</sub> was evaluated by analysis of covariance with treatment group as a factor and baseline HbA<sub>1c</sub> as the covariate, and comparison with the placebo group was carried out with a *t*-test using least square (LS) means. Here, in consideration of the multiplicity of tests between the placebo and the exenatide groups, the significance level was set to 2.5% (two-sided) with Bonferroni's method.

A dose-response relationship in the proportion of patients achieving the HbA<sub>1c</sub> target value was evaluated using the Cochran-Armitage test.

We set the sample size to be 175 patients (70 patients for each exenatide group) for the FAS in consideration of the requirement in the viewpoint of long safety evaluation<sup>11</sup>. This sample size was confirmed to ensure enough statistical power on the comparison of change in HbA<sub>1c</sub> from baseline to end-point between the placebo and exenatide 10  $\mu$ g groups.

## RESULTS

### Patient Disposition and Baseline Characteristics

Patient disposition is shown in Figure 1. Of 181 randomized patients, 179 were included in FAS. Two patients (one in the placebo group, one in the exenatide 10  $\mu$ g group) decided to discontinue before administration of the study drug. Overall,

152 patients (84%) in the FAS completed the study. The percentages of patients who discontinued after randomization were 5.6% (2/36) in the placebo group, 9.7% (7/72) in the exenatide 5  $\mu$ g group and 27.4% (20/73) in the exenatide 10  $\mu$ g group. Adverse events were the most common reason for discontinuation among exenatide patients, with nausea being the most frequent reason for discontinuation.

Patients in the FAS were generally balanced among treatment groups with respect to baseline characteristics (Table 1). Using a two-sided significance level of 15%, no significant differences were observed. Oral anti-diabetic drugs (OAD) at the time of informed consent are shown in Table 1. The most frequent combinations were SU combined with BG, and SU combined with BG and  $\alpha$ -GI.

### Changes in Glycemic Control and Bodyweight

The mean change in HbA<sub>1c</sub> level from baseline to each visit is shown in Figure 2. Reduction became apparent at week 4 in both exenatide groups and continued until week 16. Reduction was maintained at all visits after week 16 up to week 24 in both exenatide groups. The LS mean change  $\pm$  standard error (SE) in HbA<sub>1c</sub> level observed from baseline to end-point were  $-0.28 \pm 0.15\%$  in the placebo group,  $-1.34 \pm 0.11\%$  in the 5  $\mu$ g exenatide group and  $-1.62 \pm 0.11\%$  in the 10  $\mu$ g exenatide group. The changes in HbA<sub>1c</sub> level were significantly greater ( $P < 0.001$ ) in both exenatide treatment groups than in the placebo group.

The percentage of patients achieving the HbA<sub>1c</sub> target value of  $<7.0\%$  at end-point was 15.2% (5/33) in the placebo group,

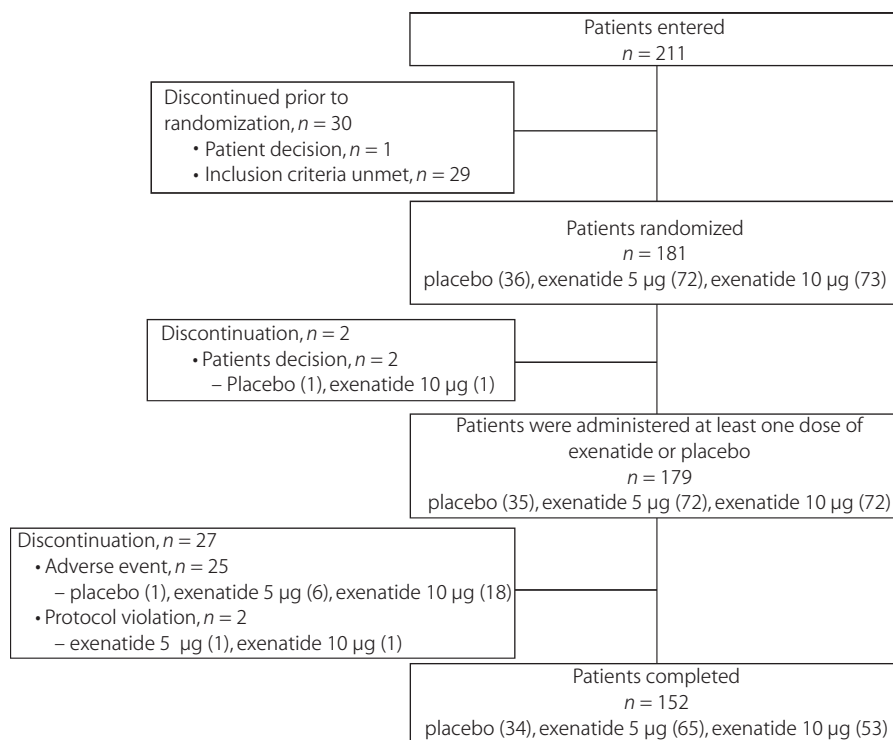


Figure 1 | Patients' dispositions.

Table 1 | Baseline characteristics

	Placebo <i>n</i> = 35	Exenatide 5 µg <i>n</i> = 72	Exenatide 10 µg <i>n</i> = 72	<i>P</i> †
Sex (male), %	24 (68.6)	49 (68.1)	49 (68.1)	0.998
Age (years)	56.3 ± 11.4	58.5 ± 9.3	59.4 ± 9.8	0.321
Weight (kg)	70.3 ± 13.3	67.0 ± 11.5	69.1 ± 11.2	0.348
Body mass index (kg/m <sup>2</sup> )	25.8 ± 4.2	25.0 ± 4.1	25.8 ± 3.9	0.391
Duration of type 2 diabetes (years)	12.4 ± 6.5	12.2 ± 6.3	11.6 ± 7.0	0.764
HbA <sub>1c</sub> (%)	8.1 ± 0.9	8.3 ± 0.8	8.2 ± 1.0	0.679
FPG (mg/dL)	160 ± 31.4	164 ± 41.5	164 ± 39.0	0.818
Total cholesterol (mg/dL)	201 ± 25.7	204 ± 35.7	202 ± 30.8	0.880
HDL cholesterol (mg/dL)	56 ± 12.5	57 ± 14.9	55 ± 10.6	0.556
LDL cholesterol (mg/dL)	123 ± 24.0	124 ± 28.3	125 ± 27.1	0.917
Triglycerides (mg/dL)	126 ± 79.2	133 ± 95.1	131 ± 69.8	0.914
Oral anti-diabetic agents at informed consent				
SU alone	3 (8.6)	4 (5.6)	8 (11.1)	
SU + α-GI	3 (8.6)	1 (1.4)	4 (5.6)	
SU + BG	14 (40.0)	33 (45.8)	27 (37.5)	
SU + BG + α-GI	9 (25.7)	22 (30.6)	13 (18.1)	
SU + BG + meglitinide derivative	0 (0.0)	0 (0.0)	1 (1.4)	
SU + TZD	4 (11.4)	6 (8.3)	12 (16.7)	
SU + TZD + α-GI	2 (5.7)	6 (8.3)	7 (9.7)	

Data are *n* (%) or means ± SD for the full analysis set. α-GI, α-glucosidase inhibitors; BG, biguanide; FPG, fasting blood glucose; SU, sulfonylurea; TZD, thiazolidine derivative. †*P* for comparison among the treatment groups.

67.1% (47/70) in the exenatide 5 µg group and 71.0% (49/69) in the exenatide 10 µg group (Figure 3). The percentage of patients achieving the HbA<sub>1c</sub> target value of <6.5% at end-point was 8.6% (3/35) in the placebo group, 36.6% (26/71) in the exenatide 5 µg group and 47.2% (34/72) in the exenatide 10 µg group (Figure 3). There was a statistically significant dose–response relationship in the proportion of patients achieving the HbA<sub>1c</sub> target value of both <7.0% and <6.5% at end-point (both *P* < 0.001).

Figure 4 shows the mean change in fasting blood glucose concentration from baseline to each visit. Marked reductions were observed at 4 weeks in both the exenatide 5 and 10 µg groups, and these reductions in mean fasting blood glucose concentration were sustained at all visits after week 4 up to the study end in each exenatide group. The LS mean change ± SE in the fasting blood glucose from baseline to end-point was −7.59 ± 5.46 mg/dL in the placebo group, −25.15 ± 3.83 mg/dL in the exenatide 5 µg group and −29.00 ± 3.81 mg/dL in the exenatide 10 µg group based on the same ANCOVA model as that used for the primary analysis. Changes in fasting blood glucose were significantly greater in the exenatide treatment groups than in the placebo group (5 µg group, *P* = 0.009; 10 µg group, *P* = 0.002).

Figure 5 shows a summary of 7-point SMBG concentration by treatment group. Reductions from baseline were observed in both exenatide treatment groups and were especially marked in the postbreakfast and postdinner blood glucose levels for patients who were in the exenatide 10 µg group.

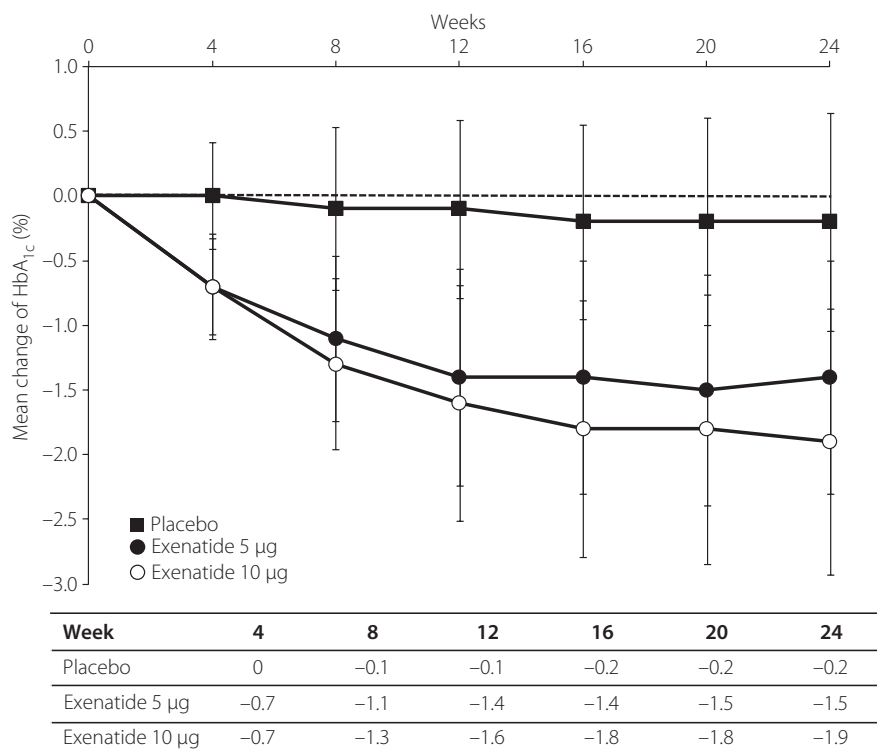
The mean ± SE changes in 1,5-anhydroglucitol from baseline to end-point were 0.66 ± 0.30 µg/mL in the placebo group,

5.29 ± 0.55 µg/mL in the exenatide 5 µg group and 4.52 ± 0.54 µg/mL in the exenatide 10 µg group. The increase in 1,5-anhydroglucitol was significantly greater in both exenatide treatment groups than in the placebo group (exenatide 5 µg, *P* < 0.001; exenatide 10 µg, *P* < 0.001).

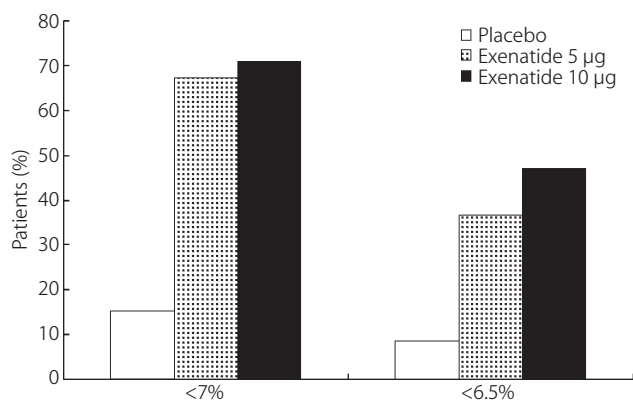
The LS means change ± SE in bodyweight from baseline to end-point were −0.47 ± 0.39 kg in the placebo group, −0.39 ± 0.28 kg in the exenatide 5 µg group and −1.54 ± 0.27 kg in the exenatide 10 µg group based on the ANCOVA model. Changes in bodyweight were significantly greater (*P* = 0.026) in the exenatide 10 µg group than in the placebo group (Figure 6).

Reductions in total cholesterol, LDL-cholesterol and HDL-cholesterol from baseline were observed in both exenatide treatment groups. The mean changes in HDL-cholesterol were −1 ± 7.1 mg/dL in the placebo group, −5 ± 7.6 mg/dL in the exenatide 5 µg group and −4 ± 5.9 mg/dL in the exenatide 10 µg group. The reduction in HDL-cholesterol was statistically significantly greater in both exenatide groups (exenatide 5 µg, *P* = 0.020; exenatide 10 µg, *P* = 0.014) than in the placebo group. No statistically significant difference was observed in total cholesterol, LDL-cholesterol and triglycerides. All changes in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were within the normal range.

HOMA-B and HOMA-R were calculated using serum insulin and fasting blood glucose. The mean in HOMA-B values at baseline were similar: 27.55 ± 24.44 (placebo), 30.87 ± 38.04 (exenatide 5 µg) and 27.96 ± 26.49 (exenatide 10 µg). The mean changes from baseline to end-point on HOMA-B were

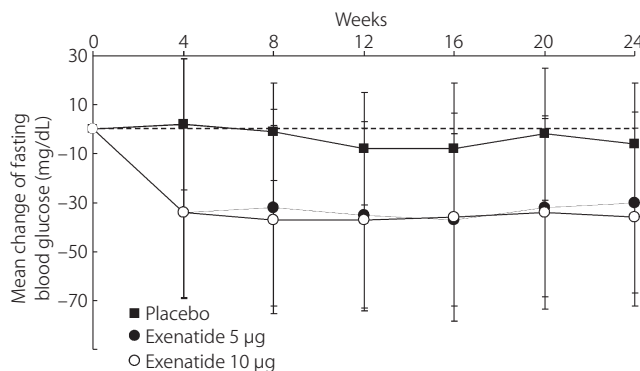


**Figure 2** | Mean changes of HbA<sub>1c</sub> from baseline to each visit. Data are mean ± SD for the full analysis set. The dotted line represents the baseline value.



**Figure 3** | Percentage of patients who received placebo, exenatide 5 µg or exenatide 10 µg achieving HbA<sub>1c</sub> <7.0% or <6.5% at end-point.

-0.71 ± 20.33 (placebo), 2.48 ± 88.40 (exenatide 5 µg) and 6.84 ± 117.59 (exenatide 10 µg). Mean HOMA-R values at baseline were 2.48 ± 1.76 (placebo), 2.86 ± 3.04 (exenatide 5 µg) and 2.58 ± 1.71 (exenatide 10 µg). The mean changes in HOMA-R at end-point were -0.38 ± 0.97 (placebo), -0.54 ± 3.37 (exenatide 5 µg) and -0.37 ± 1.59 (exenatide 10 µg). No statistically significant differences in mean HOMA-B and HOMA-R were observed between the treatment groups.

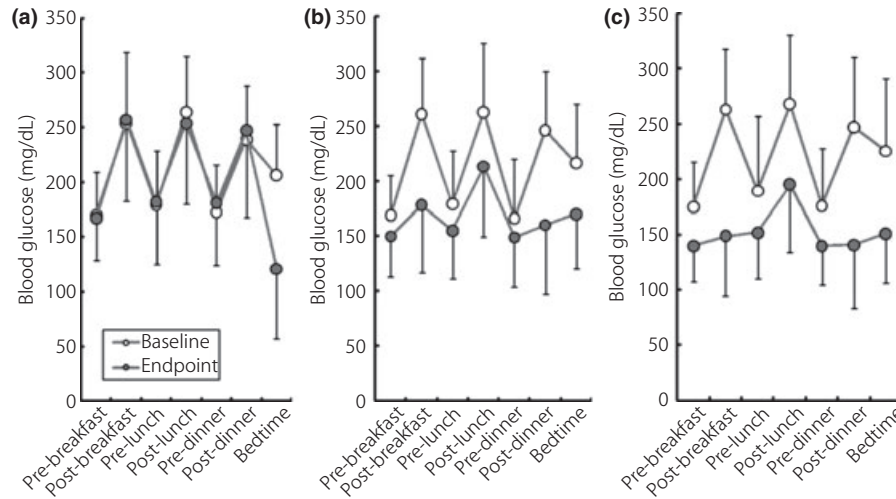


**Figure 4** | Mean changes of fasting blood glucose from baseline to each visit. Data are means ± SD for full analysis set. The dotted line represents the baseline value.

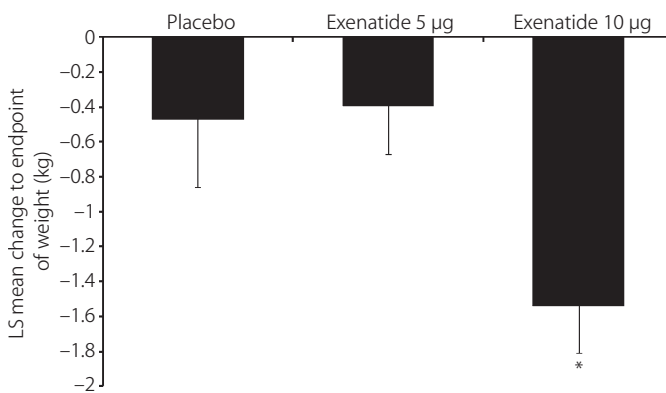
**Safety**

Serious adverse events (SAE) were reported in six patients: four patients in the placebo group and two patients in the exenatide 5 µg group. SAE in the exenatide 5 µg group were prostate cancer, major depression and diabetic ketoacidosis. No deaths occurred during this study. There were no SAE reported in the exenatide 10 µg group. The incidences of adverse events other than SAE leading to withdrawal from the study were 0.0% (0/35) in the placebo group, 5.6% (4/72) in the exenatide 5 µg group and 25.0% (18/72) in the exenatide 10 µg group.





**Figure 5** | Effects of (a) placebo, (b) exenatide 5 µg and (c) exenatide 10 µg on 7-point self-monitored blood glucose at end-point. Data are means ± SD for the full analysis set.



**Figure 6** | Change in bodyweight from baseline to end-point. Data are least square (LS) means – SE for the full analysis set. \**P* = 0.026 vs placebo.

TEAE accounted for 74.3% (26/35) in the placebo group, 97.2% (70/72) in the exenatide 5 µg group and 94.4% (68/72) in the exenatide 10 µg group. TEAE reported by >10% of patients either in the exenatide 5 µg or the exenatide 10 µg groups are shown in Table 2. Hypoglycemia, nausea and vomiting diminished over time with continued use of exenatide.

During the study, 22.9% (8/35), 51.4% (37/72) and 58.3% (42/72) of patients in the placebo, exenatide 5 µg and exenatide 10 µg groups reported hypoglycemia, respectively. With the one exception in the exenatide 5 µg group, all reported hypoglycemia were judged to be related to the study drug by the study investigators. Also, all cases of hypoglycemia were mild in severity with the exception of one case of moderate hypoglycemia in the exenatide 10 µg group. No severe hypoglycemia occurred during the study.

At end-point, 59.7% (43/72) and 44.4% (32/72) of patients in the exenatide 5 µg and exenatide 10 µg groups, respectively,

**Table 2** | Treatment-emergent adverse events with incidence >10% either in exenatide 5 µg or 10 µg group

	Placebo <i>n</i> = 35 <i>n</i> (%)	Exenatide	
		5 µg <i>n</i> = 72 <i>n</i> (%)	10 µg <i>n</i> = 72 <i>n</i> (%)
Hypoglycemia	8 (22.9)	37 (51.4)	42 (58.3)
Nausea	3 (8.6)	18 (25.0)	26 (36.1)
Blood glucose decreased	4 (11.4)	10 (13.9)	18 (25.0)
Vomiting	1 (2.9)	3 (4.2)	12 (16.7)
Constipation	1 (2.9)	10 (13.9)	11 (15.3)
Nasopharyngitis	8 (22.9)	8 (11.1)	9 (12.5)
Stomach discomfort	1 (2.9)	7 (9.7)	9 (12.5)
Appetite loss	1 (2.9)	7 (9.7)	9 (12.5)
Anorexia	1 (2.9)	2 (2.8)	8 (11.1)
Diarrhea	2 (5.7)	8 (11.1)	4 (5.6)

had detectable antibodies to exenatide (≥1/25 dilution). No relationship between anti-exenatide antibody status and overall TEAE incidence was observed, nor were any dose-dependent trends observed.

**DISCUSSION**

This is the first phase 3 study to evaluate exenatide efficacy and safety in Japanese patients with type 2 diabetes mellitus. The study shows that exenatide in combination with OAD including SU improved glycemc control, as evidenced by improvements in HbA<sub>1c</sub>, fasting blood glucose levels and postprandial blood glucose, and also reduced bodyweight over 24 weeks in patients with type 2 diabetes mellitus who were suboptimally controlled with OAD. The most commonly reported adverse events associated with exenatide treatment were nausea and hypoglycemia. No severe hypoglycemia was reported during the study.

Patients in the present study had been diagnosed with type 2 diabetes mellitus on average for 10–15 years, with mean HbA<sub>1c</sub> values at baseline of 8.1–8.3%, indicating a moderately advanced stage of type 2 diabetes mellitus. The LS mean change  $\pm$  SE in HbA<sub>1c</sub> ( $-1.34 \pm 0.11\%$ ,  $-1.62 \pm 0.11\%$ ) and FPG ( $-25.15 \pm 3.83$  mg/dL,  $-29.00 \pm 3.81$  mg/dL) observed from baseline to end-point for the exenatide 5  $\mu$ g treatment group and the exenatide 10  $\mu$ g group, respectively, were clinically meaningful and consistent with those from previous studies of exenatide b.i.d. in primarily Caucasian, Asian and Japanese populations<sup>9,10,12–17</sup>.

In the present study, both the exenatide 5 and 10  $\mu$ g groups reduced postprandial glucose (PPG) compared with the placebo group. The importance of PPG concentration in patients with type 2 diabetes mellitus has been recognized. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe study group reported that 2-h oral glucose tolerance test levels were a better predictor of on-study death from all causes and from cardiovascular disease than FPG levels<sup>18</sup>. The guideline for Management of Postmeal glucose, recently issued by the International Diabetes Federation, stated that postmeal and postchallenge hyperglycemia are independent risk factors for macrovascular disease as a major evidence statement. The guideline highlights the importance of PPG control in the context of an overall strategy to improve glycemic control as measured by HbA<sub>1c</sub> levels<sup>19</sup>.

In the current study, only the exenatide 10  $\mu$ g group significantly reduced bodyweight compared with the placebo. This apparent weight loss as a result of exenatide is important, because other anti-diabetic therapies, including SU, TZD and insulins, can cause weight gain in type 2 diabetes mellitus patients<sup>20</sup>. In some previous placebo-controlled studies of exenatide 5 and 10  $\mu$ g combined with OAD, both doses of exenatide were associated with a reduction in bodyweight<sup>13,15</sup>. This difference might be related to the difference of baseline body mass index, which was greater in the predominantly Caucasian patient population of the earlier studies (33–34 kg/m<sup>2</sup>) compared with the Japanese population of the current study (26 kg/m<sup>2</sup>). Not all exenatide-induced reductions in bodyweight are explained by gastrointestinal side-effects, as weight loss was observed in subjects who never experienced these adverse events. There was essentially no correlation between weight change and a subject's total days of nausea<sup>21</sup>.

A significant dose-dependent increase in the incidence of hypoglycemia was observed in the current study. It is reported that exenatide enhances insulin secretion in a glucose-dependent manner, wherein insulin secretion decreases as glucose levels normalize<sup>7,22</sup>. This mechanism would reduce the potential for exenatide to cause hypoglycemia. However, up to 54.9% of exenatide-treated patients reported hypoglycemia during the present study. This observation is likely because all patients were taking a concomitant SU with or without additional concomitant oral agent(s) (BG or TZD). In previous placebo-controlled studies of exenatide combined with OAD carried out in primarily Caucasian populations, concomitant SU have been implicated

in increasing the incidence of hypoglycemia when coupled with lower ambient glycemia and increasing exenatide dose<sup>12,13</sup>. Patients in the placebo arms of the present study were treated with background SU therapy (with or without additional OAD); hypoglycemia was reported in 22.9% of placebo-treated patients. Hypoglycemia was reported in 38.5% of the glibenclamide-treated patients in the study of a GLP-1 receptor agonist compared with SU for monotherapy (liraglutide and glibenclamide) in Japanese patients<sup>23</sup>. A proactive approach to SU dose management has been suggested in order to limit the incidence of hypoglycemia in exenatide-treated patients<sup>13</sup>. However, in the present study, SU was discontinued or the dose was reduced after a documented hypoglycemic episode instead of proactive SU dose adjustment. Established dose adjustment guidelines for the concomitant use of exenatide and SU in Japanese patients would be expected.

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, antibodies to exenatide were measured. In the present study, the presence of antibodies to exenatide had no clinically relevant effect.

In the present study, the average duration of diabetes was more than 10 years, which is consistent with that reported in a previous study of Japanese patients<sup>9</sup>. However, the duration of diabetes in the present study was longer than those from previous studies of exenatide b.i.d. in patient populations that were primarily Caucasian and from other Asian countries<sup>12–14,17</sup>. The difference was caused by different inclusion criteria. In the current study, patients who were receiving treatment with from one to up to three concomitant OAD were included. In contrast, in other studies, patients who were medicated with only one concurrent OAD were included.

The present study had several limitations. Patients, investigators and the sponsor were blinded to the distinction between exenatide and the placebo, but were not blinded to injection volume. A fully double-blind design might have been more robust. Also, there were no standardized diet and exercise recommendations in the current study, and we do not know what effect this additional treatment had on bodyweight changes.

In conclusion, both the 5- and 10- $\mu$ g b.i.d. doses of exenatide improved glycemic control and study results suggest that 10  $\mu$ g b.i.d. might provide the additional benefit of weight loss for Japanese patients who are suboptimally controlled with OAD. The safety profile is similar to previous studies. The current study has shown that exenatide appears to provide glycemic control benefits for Japanese patients with type 2 diabetes mellitus similar to those reported in Caucasian and other Asian patients.

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